CIRCUMSCRIBED PAN-MURAL ULCERATIVE CYSTITIS*

ELUSIVE ULCER (HUNNER)

By Floyd E. Keene, M.D.
of Philadelphia, Pa.

In 1914 Hunner presented his first report of eight cases of a rare type of bladder ulcer in women (Hunner, G. L.: *Tr. South. Surg. and Gynec. Assoc.*, 1914, 27; *Boston Med. and Surg. Jour.*, 1915, 172, 660). He has subsequently reported seventeen additional cases under the title of "Elusive Ulcer of the Bladder" (Hunner, G. L.: 1918, *Amer. Jour. of Obstet. and Diseases of Women and Children*, lxxviii, No. 3). During the past three years, ten such cases have been treated on Dr. John G. Clark's service at the University Hospital and this paper is based upon our findings in these patients.

While this type of lesion is undoubtedly rare, we are confident that it is often overlooked not only because of failure to make a careful inspection of every portion of the bladder, but also to lack of proper interpretation of the findings which in the earlier cases may show very little variation from the normal so far as gross changes are concerned. In looking back over our own experience in cystoscopic work, we recall cases that were doubtless of this type, in which the condition was overlooked completely, or, recognizing it, we failed to direct appropriate treatment for its cure.

This error was forcibly impressed upon us by a case, long under our care, who finally consulted and was operated upon by Doctor Hunner; at operation he demonstrated, without question, the extent of disease and the complete cure in this case left no doubt as to the wisdom of his teaching regarding the value of excision.

Hunner has described the condition under the name of "Elusive Ulcer," choosing the term to designate the difficulty often experienced in locating the ulcer. Such a nomenclature seems unsatisfactory in that it gives no conception of the pathology and, in fact, may be misleading in that it magnifies the importance of the ulcer which in reality is a small part and but an end result of an inflammation involving a considerable portion of the entire bladder wall. The lesion brings to mind a type of disease which Nitze calls Cystitis Parenchymatosa (Knorr: *Die Cystoskopie und Urethroskopie beim Weibe*, p. 211), in which not only the mucosa but the submucosa and muscularis participate, and until recently we have spoken of the lesion we are about to describe as a circumscribed parenchymatous ulcerative cystitis. Dr. Allen J. Smith has suggested

* From the Department of Gynecology, University of Pennsylvania. Read before the Philadelphia Academy of Surgery, January 5, 1920.

that the word " pan-mural " be substituted for " parenchymatous," pointing out the fact that the former is more accurate in its application to the pathology of the bladder as well as more descriptive of the extent of the inflammation, and we have followed his suggestion.

Pathology.[1]—Grossly, the lesion is characterized by more or less thickening of the entire bladder wall with œdema and minute, superficial ulceration of the mucosa. The disease is practically always limited to the vertex of the bladder, although rarely it may extend downward and laterally on one or both sides to within a few centimetres of the trigone. The amount of bladder wall involved varies considerably; of our operative cases, the tissue removed ranged from 2 by 3 centimetres to 7 by 7 centimetres. The disease is never " patchy " in distribution, but is limited to one section of the bladder. The bladder wall is distinctly firmer than normal and in two of our cases the induration could be detected on bimanual examination. The inflammation may extend beyond the bladder confines, not infrequently involving the paravesical tissues and adjacent peritoneum. Such a paracystitis is most commonly found in association with and in the immediate vicinity of a comparatively large ulcer.

The mucosa is thickened and œdematous and with proper illumination the diseased area stands out in sharp contrast with the normal bladder. The ulcers may be single or multiple; in our series the latter has occurred more commonly, but in no case have we found more than three. The areas of ulceration are always minute and very superficial; because of this one may at first glance have difficulty in locating them. The ulcer usually presents a clean, bright red surface with sharply cut edges. The lightest touch with a cotton-covered probe will be followed immediately by bleeding.

Microscopically, the picture is that of an inflammation involving the entire bladder wall and paravesical tissues. The bladder wall is thickened, due in small part to fibrous tissue, but largely to loosening of the intermuscular and paravesical connective tissue incident to œdema. Within the areas of ulceration, the inner surface of the mucosa fails to show the presence of the ordinary epithelium; the basement membrane is, as a rule, well marked and is often somewhat thickened. Immediately beneath the basement membrane in the non-ulcerated portions are areas of dense round-cell infiltration, consisting mainly of lymphocytes and plasma cells. Where there is loss of the surface epithelium, the fibrous tissue is very loose and is filled with polymorphonuclear leucocytes.

The deeper part of the submucosa may be fairly free from an inflammatory exudate and shows little change save loosening from œdema, but its blood-vessels often stand out prominently, due to the number of polymorphonuclear leucocytes which are seen not only within the lumen,

[1] I am greatly indebted to Dr. Allen J. Smith and Dr. Charles C. Norris for their interest and assistance in the study of these sections.

FIG. 1.—Cystoscopic picture showing diseased area above and normal mucosa with ureteral orifices below. Intense congestion about three small, superficial ulcers which are situated in lower portions of the œdematous zone. Section excised measured 7 x 7 x 4 cm. The disease was located in the vertex of the bladder, but is here shown near the base in order to demonstrate the essential features in one drawing.

but infiltrating the vessel walls and perivascular tissues. Here mononuclear cells are fairly rare, only an occasional large mononuclear being seen.

The same vascular and perivascular polynuclear invasion affects the blood-vessels in the muscular and outer coat, being often very marked in the latter, so that a leucocytic thrombus is in many instances apparent, and the leucocytic involvement of the coats is such that one would speak of an acute exudative arteritis and phlebitis. The appearance is given that the lymph channels are similarly affected. Foci of round-cell infiltration likewise occur in the muscle fascicles, but no degenerative changes have been observed.

Cystoscopic Picture.—The picture presented by the cystoscope (Fig. 1) is fairly typical in most cases, and having seen one or more, the observer is immediately aware of the fact that he is in all probability dealing with an ulcer-bearing area. The most striking feature is œdema of the mucosa, localized in the vertex of the bladder. The œdematous area is somewhat hazy, there is an absence of sharp definition of the vessels, or the vessels may appear unduly short, seeming to suddenly appear in the field, and after a short distance, completely disappear from view. Or they may be seen in small clusters, giving a "flea-bite" appearance in one or more areas.

The mucosa has lost its normal golden-white, glistening surface, and has assumed a more or less diffuse, dull pink color. Occasionally one sees elongated, elevated areas of mucosa which give the appearance of scar tissue, and in one of our cases two small ulcers were mounted at the summit of such an area. With a well distended bladder and good illumination, one can make out very clearly the sharp line of demarcation between the normal and œdematous mucosa.

The ulcers give the appearance of minute areas of healthy granulation tissue, the base being a deep red color and rarely covered with fibrin. Through the cystoscope the ulcers stand out even more plainly than with the naked eye; they present sharply cut edges and are always superficial, appearing as if minute areas of mucosa had been removed with a sharp curette. They are always small, varying in our cases from 1 by 2 mm. to 4 by 5 mm. Surrounding the larger ulcers is an area of intense congestion and œdema which the smaller ulcers often lack. As has been our experience in two cases, the ulcers may show active bleeding. Touching the ulcer with a catheter or probe at once produces bleeding, and the patient will complain of sharp pain. The bladder base, including the trigone and ureteral orifices, is always normal in appearance; not uncommonly, as the result of frequent urination, papillary hypertrophy of the internal sphincter is present.

Symptoms.—An analysis of the symptoms presented by our patients gives one common to all—bladder pain with intense urgency and frequency of urination. In the most severe cases the bladder must be emptied every few minutes, with pain during, but more especially after,

urination. Often the dysuria is exaggerated at night, but the reverse may be true. There is an associated intense urgency, so that the patient finds it next to impossible to hold the urine. Not infrequently the pain is located in the lower abdomen, usually just above the symphysis on one or both sides of the median line. This is doubtless due to an extension of the inflammation to the peritoneum and the pain may closely simulate that of a chronic pelvic peritonitis or appendicitis. The pain may be localized to the bladder and lower abdomen or may be referred; in one of our cases intense rectal discomfort was complained of, in another a sensation of " spasm " in the perineal region, and Hunner calls attention to the frequency of referred pain in one or both hips, depending on the location of the ulcer. The severity of symptoms, of course, varies in different patients, and in several instances we have noted more or less of a periodicity of exacerbations and remissions, lasting several weeks and entirely independent of treatment. That this is not due to healing of the ulcers is evident from the fact that the remission occurs with no apparent change in the appearance of the bladder. As is so frequently the case in inflammation of the bladder, premenstrual congestion exaggerates the symptoms. The symptomatology is usually one of long standing; in our series the duration varied from six months to fourteen years, and the average is about four years.

As the result of years of bladder trouble, these patients have been under more or less constant medical attention and are consequently well versed in their urinary findings. As a rule, they report that the urine was found to be normal, but in two of our cases a history of hæmaturia was given. The bleeding is of short duration, lasting only a day or so, and then completely disappears, at least on gross examination.

Microscopic examination of the urine may be normal with the exception of a slight excess of leucocytes and a few red blood-corpuscles. In only two of our cases were many leucocytes reported. One case came to us with macroscopic hæmaturia which was found to originate in a small ulcer, two others showed a few red blood-cells in the centrifuged specimen, while the remainder showed none. A grossly normal appearing urine with the presence of a few leucocytes and red blood-cells may be said to be characteristic of the majority of these cases.

Etiology.—We are at a loss thus far to explain the cause of this condition, but believe with Hunner that it is due to an infection, probably hæmatogenous in origin. The tubercle bacillus is certainly not responsible. In no case has it been demonstrated microscopically nor by guinea-pig inoculation; nor is there anything in the cystoscopic picture or the sections of the bladder suggesting tuberculosis. Hunner seems inclined to ascribe the inflammation to an infection secondary to such a focus as tonsils, teeth, or sinuses; we have made it a special point to determine this possible etiology, but without success. In two of our cases the patients date the onset of symptoms from repeated catheterization, one

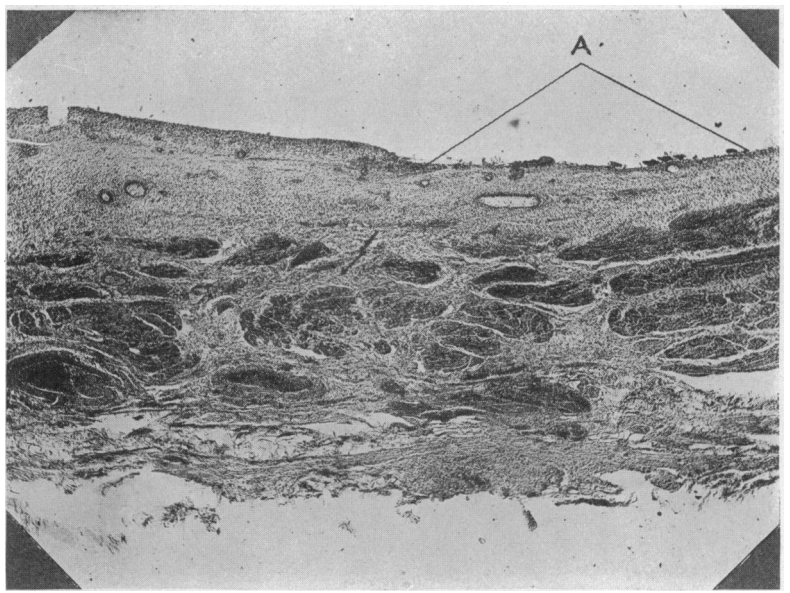

FIG. 2.—Section of bladder wall, showing ulcer at *A*. Numerous areas of round-cell infiltration in submucosa. Œdema shown by looseness of muscularis. Only slight increase in connective tissue.

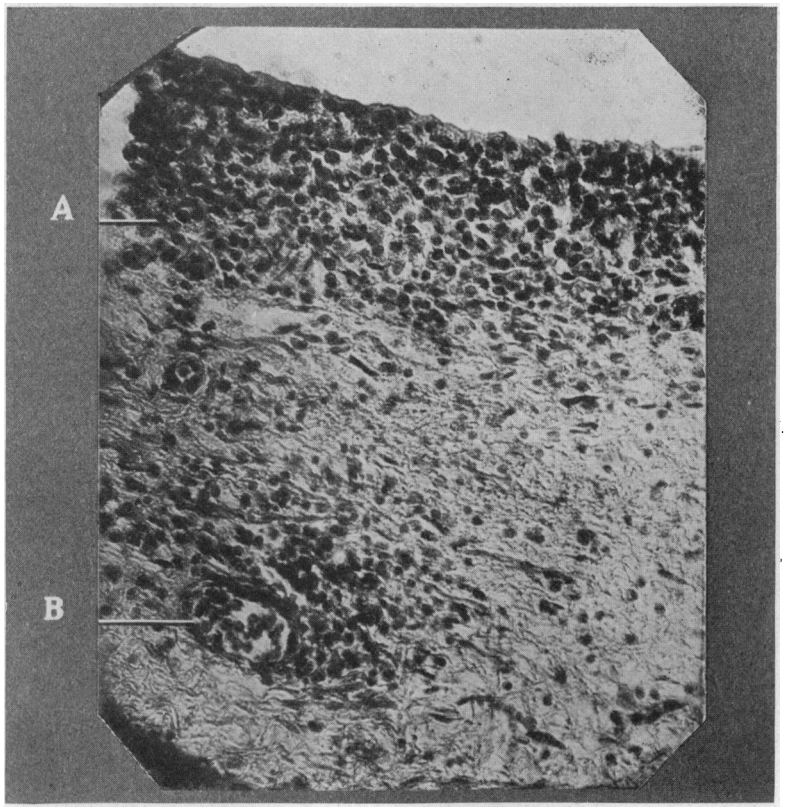

FIG. 3.—*A*, Mucosa in non-ulcerated area. Infiltration of round cells composed almost entirely of lymphocytes and plasma cells. *B*, Blood-vessels in submucosa filled with polymorphonuclear leucocytes, with perivascular infiltration.

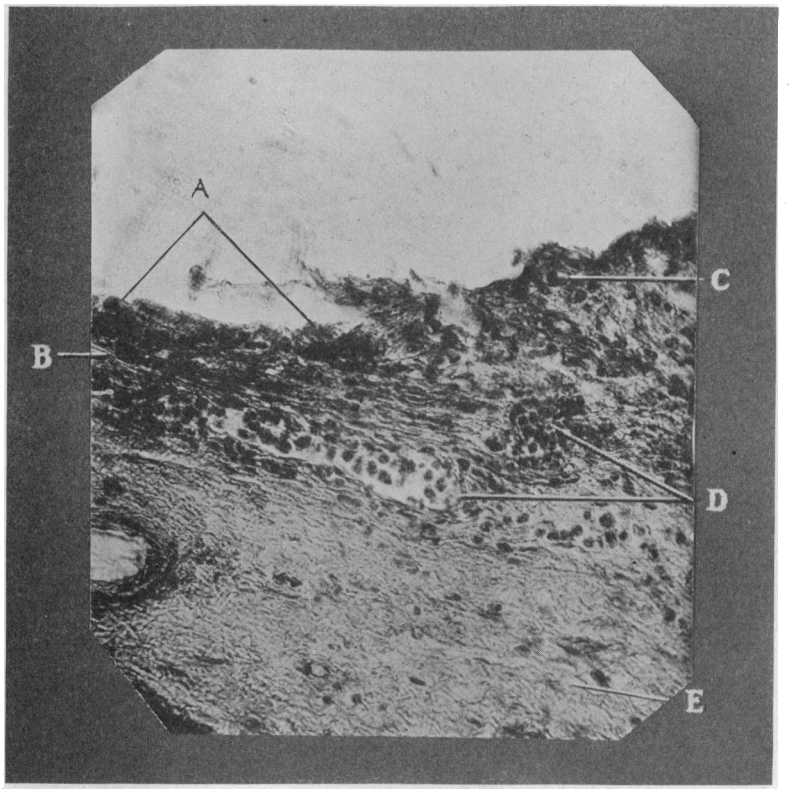

FIG. 4.—*A*, Base of ulcer showing absence of epithelium. *B*, Thickened basement membrane. *C*, Epithelium at edge of ulcer. *D*, Blood-vessels filled with leucocytes. *E*, Œdema of submucosa.

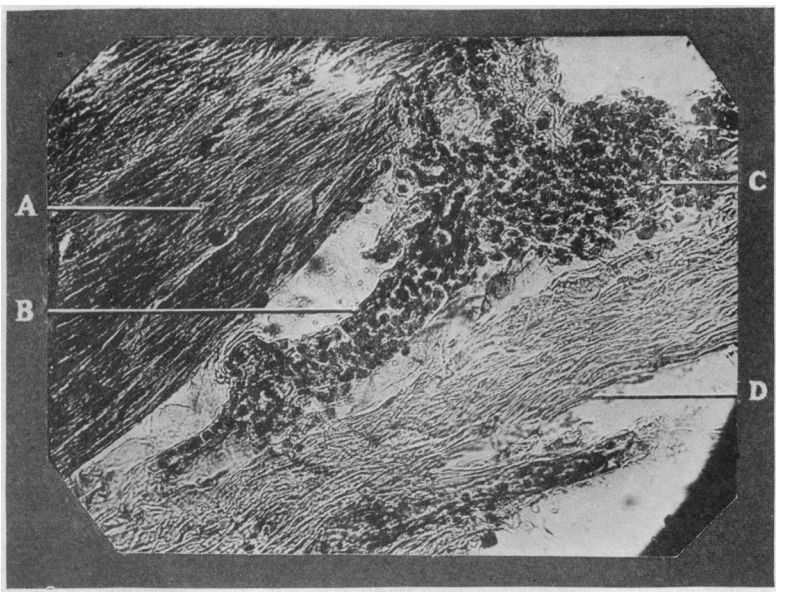

FIG. 5.—Taken from centre of muscular layer. *A*, Muscle. *B*, Large blood-vessels filled with polymorphonuclear leucocytes which can be seen invading vessel wall. *C*, Perivascular infiltration. *D*, Connective tissue.

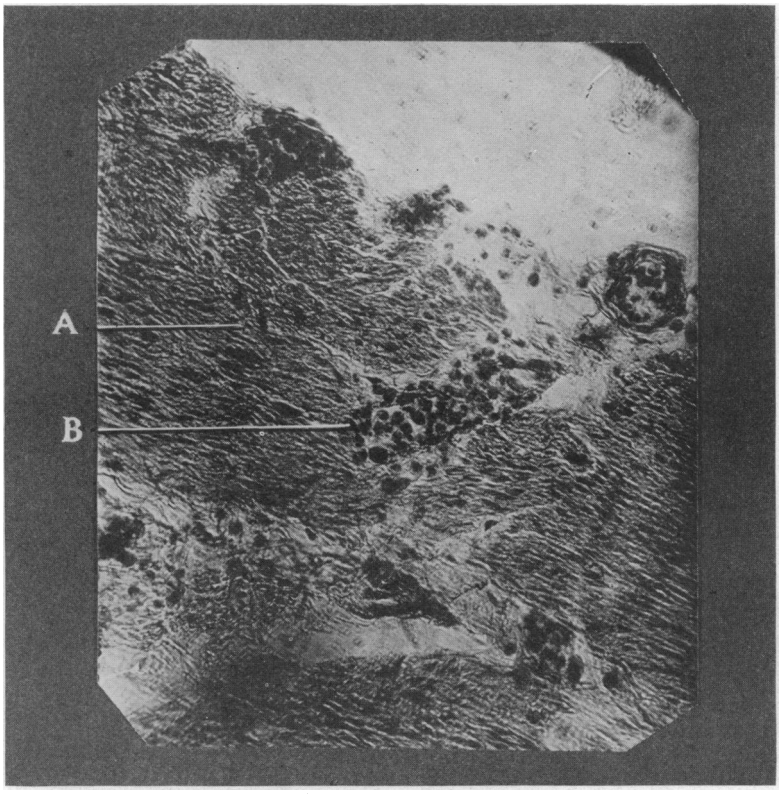

FIG. 6.—Taken from fibrous coat of bladder. *A*, Fibrous tissue. *B*, Blood-vessels filled with polymorphonuclear leucocytes which can be seen within the vessel wall. Also perivascular collection of leucocytes.

during an attack of typhoid fever, the other following an operation. The remainder can ascribe no probable cause.

In none of our cases has there been any evidence whatever of a gonococcal infection. The condition is not secondary to inflammatory disease of the pelvic organs, for no such condition has been demonstrated either by vaginal palpation or intra-abdominal examination. From the fact that the pathology is always limited to or is most extensive in the bladder vertex, one might consider the possibility of its being associated with disease of the urachus, but we have found no evidence of this.

Hunner reports a sterile urine in his cases; such has not invariably been our experience. In one there was a pure culture of colon bacilli, in another staphylococci and non-hæmolytic streptococci. In three the urine was sterile, while in the remaining cultures were not made.

An analysis of the clinical and pathological findings suggests the possibility that a paracystitis may be the primary lesion, and that the changes seen in the bladder itself are purely a secondary manifestation.

Treatment.—We have run through the gamut of local applications in our treatment of these cases and have come to the conclusion that Hunner is correct in his statement that " no form of treatment will suffice except complete excision of the inflammatory area." As previously stated, certain cases show periods of improvement lasting several weeks, which seem to be in no way dependent on treatment. Again, the symptoms may be somewhat relieved by applications of silver nitrate, silver iodide, carbolic acid, etc., but the relief is only temporary and nothing short of excision has in our hands given a permanent cure. We have not tried fulguration, but Hunner reports two cases in which this treatment produced such severe pain that the patients refused further applications; he has also used the actual cautery wire which seemed to lessen the symptoms somewhat, but did not cause healing of the ulcers.

Operative Treatment.—The operation consists in excision of the diseased area of bladder wall, and the limits of excision are determined not by the ulcerations, but by the distinctly outlined œdema. Anything short of this will result in failure.

Through a suprapubic incision, the bladder is exposed and opened, if possible, at a point previously determined by cystoscopic examination to be outside the area of œdema. The opening in the bladder is made sufficiently large to give a good exposure of its interior and the greatest care is exercised in handling the bladder to avoid an artificial œdema incident to trauma. By means of an illuminated vesical retractor, it is an easy matter to determine the limitations of the œdema, and these are marked by a series of linen traction sutures, passed deeply into the bladder wall to prevent their cutting out. Small ulcers which were plainly seen through the cystoscope in a well-distended bladder may at operation be difficult to locate at first glance. They appear as small, red spots which bleed easily on being touched with a cotton-covered probe.

After placing the traction sutures, the bladder is freed as much as necessary and the area outlined by the sutures is excised. Ideally, the operation should be extraperitoneal, but occasionally, in spite of care, the peritoneum will be opened during separation of the bladder; we have seen no ill results follow. After complete hæmostasis has been obtained the bladder is closed with a two-layer suture of catgut, the first being submucous, the second intramuscular, and both of the Cushing type. A suprapubic drain is placed in the bladder through an angle of the incision, and a Mikulicz drain is placed in the prevesical space, well away from the suture line in the bladder wall.

Post-operative Treatment.—The Mikulicz drain is removed in forty-eight hours, the bladder drain at the end of ten days. The bladder is irrigated daily through the drain, with a catheter in the urethra to avoid the danger of over-distention. After removal of the tube we have found it advisable to continue the bladder irrigation, using a weak silver solution, until the healing is complete. The patient is instructed to retain the urine as long as possible in order to hasten the restoration of the bladder to its normal capacity, which requires, as a rule, about two months.

Results.—Eight of our cases have been operated upon, one by Doctor Hunner and seven by Doctor Clark. In all of these, various methods of treatment were tried and in none was more than a temporary lessening of symptoms obtained.

The first case, who had been under our care for some time, consulted Doctor Hunner, who operated upon her two years and a half ago; this patient is cured after many years of intense bladder symptoms. The time since operation in our cases is as follows: Case I, two and one-half years; Case II, two years; Case III, twenty-three months; Case IV, twenty-one months; Case V, sixteen months; Case VI, nine months; Case VII, three months; Case VIII, two months. We have followed the post-operative course of these patients very carefully and have a written or verbal report of all up to date. Seven have been cured, and in each the bladder capacity has been restored to normal. Case II had a urinary fistula at the site of the suprapubic drain for several months, but this has closed and the patient is now free from bladder symptoms. Case III was well for seven months when the symptoms returned during a severe attack of influenza. She has a recurrence of the œdema and ulceration on the left side of the bladder vertex and is returning to the hospital for a second operation.

In no series of cases that we have studied has greater appreciation of what an operation has done for them been shown than in the seven who have been cured. We have recently had the opportunity of making a cystoscopic examination of four of these patients, and the bladder in each presented a normal appearance with the exception of a thin scar line at the site of excision.

Non-operative Cases.—Case IX was examined two years ago on account of severe vesical symptoms. She had a myoma uteri the size of a two months' pregnancy and a typical lesion in the vertex of the bladder, with marked œdema and a single ulcer located in the median line, one inch posterior to the internal sphincter. She later consulted a surgeon in a neighboring city, who ignored the bladder findings and ascribed her symptoms to pressure of the tumor. A hysterectomy was performed, and at our last report there has been no relief of the urinary symptoms.

Case X has only recently been under observation. She was admitted to the hospital complaining of frequency and urgency of urination, with pain low down in the left side of the abdomen, referred to the left hip. On cystoscopic examination, œdema of the left bladder vertex was found, with an ulcer situated one inch to the left and one inch behind the left ureteral orifice, which is the first instance in our experience of ulceration near the base. Under confinement in bed and silver nitrate applications, the symptoms lessened, but the ulcer remained the same. Contrary to advice, she insisted on going home, and in a recent letter from her physician we learn that the symptoms have recurred with such severity that she desires to return for operation.

Summary.—1. Circumscribed pan-mural ulcerative cystitis is a distinct pathologic entity, characterized clinically by its chronicity, intense vesical symptoms, and a urine, usually sterile, containing a slight excess of leucocytes and a few red blood-cells; pathologically, by its location in the vertex of the bladder, presenting a sharply demarcated area of œdema with one or more small, superficial ulcers within this œdematous area. The inflammation affects the entire bladder wall and may involve the adjacent peritoneum.

2. The etiology is as yet undetermined, but it is probably due to infection of hæmatogenous origin.

3. Intravesical applications are of value only in giving partial and temporary relief. The best method of treatment consists in excision of the diseased bladder wall, the limits of which are determined by the extent of the œdema.